Comparison of triamcinolone acetonide mucoadhesive film with licorice mucoadhesive film on radiotherapy-induced oral mucositis: A randomized double-blinded clinical trial

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Abstract

Aim: Mucositis is a major complication of irradiation in head and neck tumors, the addition of chemotherapy to irradiation may enhance this dose-limiting problem. Licorice is a strong demulcent that had been effectively used in treatment of peptic ulcer. The main purpose of this study was to compare the therapeutic safety and efficacy of triamcinolone acetonide (T) and licorice (L) mucoadhesive films on oral mucositis in terms of pain control and/or ulcer treatment.

Methods: The study was a double-blind, randomized prospective trial of two types of mucoadhesive films in the management of oral mucositis that occurred during head and neck cancer radiotherapy. Oral mucositis was assessed using a quantitative scale (World Health Organization scales) and symptoms were assessed using visual analog scale. Sixty patients were enrolled in the study: 30 patients in the triamcinolone and 30 in the licorice group.

Results: With respect to visual analog scores, repeated observations in consecutive weeks showed a meaningful difference (P-value < 0.05), suggesting the efficacy of both T and L in reducing pain during radiotherapy. Comparison of the pain scores between two groups by independent sample t-test, however, demonstrated no meaningful difference in any consecutive week.

Conclusions: We concluded that both triamcinolone and licorice mucoadhesive films are effective in the management of oral mucositis during radiotherapy. Furthermore, comparison of the pain scores between two groups demonstrated no meaningful difference, although an overall trend to reduced oral discomfort was seen in the licorice group.

Key words: irradiation, licorice, mucoadhesive film, oral mucositis, triamcinolone acetonide.

INTRODUCTION

Both radiation and chemotherapy are important modalities used in the treatment of head and neck cancer (HNC). The cytotoxic effects of these therapies are not only limited to tumor cells, but also act on normal tissues with a high cell turnover. The oral mucosa (OM) represents a cellular compartment that possesses a high rate of cellular turnover. Disruption of the mucosal lining is associated with radiation therapy as a direct effect, and as a secondary effect due to enhanced effects of physical, chemical and microbial insults in the mouth. Mucosal breakdown is painful and may interfere with oral function including drinking, eating, speaking and denture function, and may predispose to infection of the mucosa and provide a portal for systemic infection.1-5

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The resulting oral ulcerative lesions can cause significant pain, dysphagia, alteration in nutritional status and increased risk for localized infections that could disseminate systemically.\textsuperscript{6,7} The severity of mucositis induced by radiation therapy depends on a number of factors including the administered dose, the dose fraction, the volume of tissue treated and the type of radiation given. Other factors that may contribute to the severity of mucositis include continued smoking, the use of alcohol-based mouth rinses, and the presence of collagen vascular disease and HIV infection.\textsuperscript{8–12}

Erythema is the initial manifestation followed by the development of white desquamative patches that are painful on contact. Epithelial cell loss also results in the exposure of the richly innervated underlying connective tissue stroma which contributes to the pain associated with the more severe forms of mucositis.\textsuperscript{5,6}

The morbidity of oral mucositis can be profound. It is estimated that approximately 15\% of patients treated with radical radiotherapy (RT) to the oral cavity and oropharynx will require hospitalization for treatment-related complications. In addition, severe oral mucositis may interfere with the ability to deliver the intended course of therapy, leading to significant interruptions in treatment, possibly impacting on local tumor control and patient survival.\textsuperscript{5–7}

OM is associated with a range of acute and chronic symptoms that exert a substantial negative impact on quality of life. Persistent eating difficulties can lead to weight loss, anorexia, cachexia and dehydration, leading to the need for parenteral feeding. Patients have also attributed increased depression and sleep disturbances to OM. OM is also associated with substantial clinical and economic consequences. It increases the duration of hospitalization as well as the frequency of liquid diet, fluid replacement, total parenteral nutrition, opioid use, and antibacterial, antifungal and antiviral use.\textsuperscript{13–17}

Although the adverse effects of RT and chemotherapy cannot be totally avoided, there are ways to minimize the side effects of these treatment procedures. Therefore, an attempt has been made to minimize the radiation-induced mucositis, skin reaction, xerostomia, change in voice, etc. with a mucoadhesive preparation, that is, licorice (\textit{Glycyrrhiza glabra}) compared with triamcinolone acetonide. Furthermore, we have tried to assess the efficacy of the prepared drugs in the healing of the above said side effects.

Sometimes called the great harmonizer, licorice root has a long history of use in Chinese medicine for a variety of conditions dating back to at least 500 BC. For some people, the glycyrrhizin component of whole licorice can cause adverse reactions. However, a unique extract called deglycyrrhizinated licorice (DGL) is free of glycyrrhizin. DGL has had no significant reported adverse effects. It therefore avoids the adverse reactions of whole licorice, but retains its beneficial qualities.\textsuperscript{18–20}

Modern medical history of licorice root begins in 1946, with the first article about “licorice juice” for gastric ulcers. While DGL is popular for relieving gastric irritations, clinical trial support is weak.\textsuperscript{21}

The objective of this study was to compare the efficacy of triamcinolone acetonide mucoadhesive films with licorice mucoadhesive films in the treatment of mucositis and relief of pain associated with radiation therapy involving the oropharyngeal region.

\section*{MATERIALS AND METHODS}

\subsection*{Study design and intervention}

This study was a double-blind randomized trial (ClinicalTrials.gov Identifier: NCT02075749) designed to compare the safety and efficacy of triamcinolone acetonide mucoadhesive films with licorice mucoadhesive films in treating OM in HNC patients undergoing postoperative adjuvant or definitive RT. Between June 2013 and February 2014, a total of 60 HNC patients in a university hospital were randomized to standard oral care plus T (30) or L (30) taken four times daily (applied upon the upper lip mucosal surface). Treatment began when mucositis with World Health Organization (WHO) scales 2 and 3 was diagnosed and continued for 4 weeks. Safety and efficacy assessments were based on adverse events, physical examination, laboratory determinations, vital signs, WHO scores, the ability to eat, body weight change, local control and survival.

\subsection*{Eligibility criteria}

All inclusion criteria were required before entry into the trial. These criteria were: over 18 years of age, with documented histologic diagnosis of HNC, and grades 2 and 3 oral mucositis (as defined by the WHO scale). The severity of OM is commonly assessed by clinicians using the WHO Oral Toxicity Scale, which is based on both objective and subjective criteria (Table 1),\textsuperscript{8} men and nonpregnant women or women of childbearing age who were nonpregnant by pregnancy test and using medically prescribed contraceptive, and an ability to remain in the study for its entire duration.
Exclusion criteria were: pregnant women, concurrent chemotherapy, a history of heavy alcohol or drug abuse judged to be important by the investigator, concomitant therapy with an investigational drug, or cancer chemotherapeutics or immunosuppressive medications. Sensitivity or intolerance to the drug ingredients, lactose or similar formulations, inability to provide informed consent, actively bleeding gastric ulcer, severe esophageal reflux, major surgery, trauma or burns in the preceding 4 weeks, and clinically significant hepatic, neurologic, endocrine or other systemic diseases make implementation of the protocol or results difficult. Patients were also excluded if they had used investigational drug within 30 days before enrollment of this study. A medication compliance of less than 70% and a visit compliance of less than 70% were also considered as dropout criteria.

**Endpoints**

There were two principal endpoints. The first was the safety of the studied mucoadhesive films measured as the incidence of reported adverse events, abnormal physical and oral examination findings, laboratory determinations, and vital signs throughout the study. The second endpoint was the efficacy of studied drugs measured as the incidence, severity and duration of OM.

**Treatment plan**

RT was delivered in a two-dimensional cobalt-based technique. It was irradiated with 5600–6000 cGy in 28–30 fractions, daily 200 cGy per fraction. Following informed consent, patients who met the eligibility criteria were randomized to one of the two treatment groups after the occurrence of WHO grades 2 and 3 mucositis (Appendix I), which were mostly observed at the second week after the initiation of RT. The head and neck (H&N) RT normally did take 5–6 weeks, and the duration of the study (i.e. mucositis management with mucoadhesive films) was also about 4 weeks or until complete remission. As a result, RT and mucositis management were nearly completed simultaneously. One group received standard oral care plus T applied four times daily (each film containing 0.5 mg triamcinolone acetonide); the other group received standard oral care plus L (each film containing 0.18 mg polyphenols as pyrogallol extracted from licorice root). The standard oral care included frequent rinsing of the mouth with boiled water, regular toothbrushing and flossing habits, scaling, and plaque and tartar removal during the course of RT.

Patients or caregivers were given the instruction on how to use the study medications correctly. Furthermore, they were not allowed to use any forms of analgesics or painkillers (e.g. paracetamol, lignocaine gel, non-steroidal anti-inflammatory drug or liquid morphine) before or during the study so as to prevent misinterpretation of VAS (visual analog scale) score assessed by investigators.

After obtaining the patient’s subjective assessment, clinical examination was performed through clinical examination and independent rating of severity of mucositis by two investigators independently, and the ascertainment of fulfillment of eligibility criteria, randomization to treatment arm T or L, was performed without further stratification and according to a balanced block randomization procedure by a third investigator who had no information about rating of severity preceding or current results of the two available treatment modalities within the present trial. In order to ensure advanced homogeneity of patient groups participating in the experimental and control groups, and to exclude factors that could decrease the efficacy of the mucoadhesive application before the application of the drugs, a questionnaire form was used for each of the 60 patients, which included socio-demographic, individual and illness-specific features.

Both treatment modalities were stopped in case of complete response, but continued for another period of 7 days in case of improvement without the complete resolution of symptoms and/or lesions, respectively. Treatment was discontinued in case of severe side effects or upon the patient’s request.

**Measurements (evaluation methods)**

Data were collected using a form prepared by the researchers, which contained questions regarding gender, education level, presence of a systemic disease, cigarette use, nutrition, dentist visits prior to treatment, receipt of mouth care education, toothbrushing habits, presence of prosthesis, mouth dryness, loss of appetite, cancer stage and length of disease. In addition, the
WHO Mucositis Scale (Table 1) was used for the oral mucositis assessment of the patients. The patients were asked to place a mark corresponding to the degree of oral mucositis at the beginning of treatment (day 1). Compliance was assessed by counting of used and unused films that were returned weekly. Patients were evaluated weekly.

Symptoms were assessed using VAS. Pain intensity was verified using a 10-cm (100-mm) VAS anchored by “no pain” at one end and by “worst possible pain” at the opposite end. The VAS, after teaching the patient as to determining their pain score visually or numerically, was used to evaluate pain, with the patient attributing a value that corresponded to the level of his or her pain. The threshold for efficient analgesia was defined as a 13-mm decline from the baseline VAS. The statistically significant analgesia, however, was held to be a VAS score of 30/100 or lower. Symptoms evaluated by VAS were soreness/burning, pain on waking, pain with drinking, pain with speaking, pain upon swallowing, dry mouth, burning with use of the study medications and taste of the medication. Patient’s use of caffeine-containing products, tobacco and alcohol was noted. Safety was assessed by physical examination, clinical laboratory testing of hematology (red blood cell count, indices, hemoglobin, hematocrit, white blood cell count, and differential and platelet count), biochemistry (blood urea nitrogen, creatinine, alkaline phosphatase, serum glutamic oxaloacetic transaminase, lactate dehydrogenase, total protein, albumin and electrolytes), urinalysis (pH, specific gravity, protein, glucose, ketones, microscopic examination) and adverse experience evaluation.

Ethical consideration
Oral consent was obtained from the patients for their participating in the study before the questionnaire forms were administered. The patients were also informed of the study verbally. Participation was voluntary and the patients could withdraw from the study at any time without giving a reason. Approval was obtained from Ethics Committee of the Isfahan University of Medical Sciences.

Statistical analysis
The data were recorded and analyzed using Statistical Program for Social Sciences version 18.0 for windows (SPSS Inc., Chicago, IL, USA). For the analysis of data, analysis of variance (ANOVA), independent sample t-test, and Friedman and Mann–Whitney tests were used. Statistical significance levels were set at $P < 0.05$.

RESULTS
Sixty patients were found to be eligible for this study. The T group included 18 (60%) males and 12 (40%) females with a mean age of 58.53 ± 8.89. The L group involved 19 (63.3%) males and 11 (36.7%) females with a mean age of 57.33 ± 10.05, which suggests no statistically significant difference between two groups in terms of age and gender. In other words, with regard to age and gender, two groups were similar ($P > 0.05$) (Table 2). The mean value of pain score among patients of the two groups during 4 consecutive weeks assessed by ANOVA test with repeated observations showed a meaningful difference ($P < 0.05$), suggesting the efficacy of both triamcinolone acetonide and licorice mucoadhesive films in reducing pain during RT. Comparison of the pain scores between two groups by independent sample t-test demonstrated no meaningful difference in any consecutive week. And although an overall trend to reduced oral discomfort was seen in the licorice group, it was not statistically significant ($P > 0.05$) (Table 2, Fig. 1).

The mean value of mucositis scale during 4 consecutive weeks assessed by Friedman’s test depicted a meaningful difference ($P < 0.05$), which means during RT the use of both T and L mucoadhesive films may have a notable effect upon the grading of mucositis. We also compared the individual mucositis scale between two groups in consecutive weeks. And again, despite the lower mucositis grading that occurred in the licorice group, no statistical difference between T and L groups regarding mucositis pain relief and anti-inflammatory effects was noted (Table 2, Fig. 2).

DISCUSSION
Unfortunately, research to date has not been able to identify a universal effective intervention for the prevention and treatment of mucositis. Using a standard approach based on the current evidence is therefore recommended.

The management of oral mucositis remains a challenge. Failure to palliate this distressing symptom can lead to the use of potentially harmful self-care measures. This may be avoided by thorough assessment, the implementation of standard care and developing individualized care plans to improve patient outcomes.22

To deliver a medication in the mouth over time for treatment of health problems in the mouth or throat, oral patches have been developed. An oral patch typically includes one or more flexible layers that do not dissolve entirely.23,24
The most significant difference between an oral patch as used herein and other forms of medicinal preparations is that an oral patch is designed to release medication into the mouth over a relatively long period of time, such as 30 min or more, and be adherent to stay in one place so that the medication can reach high concentrations alongside the patch, and remain in the mouth as a single item that will not spread to be in a plurality of location in the mouth at one time.20

Complementary and alternative medicine (CAM) had proven efficacy in pain relief, correction of nutritional status and improving the performance status. However, lack of standardization is the major obstacle for any scientific evaluation of any CAM trial.21

DGL is specifically used to promote the healing of ulcers and reduce ulcer-related symptoms. While it appears to be efficacious in this regard, the only clinical trials published using DGL as a treatment are poorly designed and/or were conducted more than 20 years ago.18–20

To the best of our knowledge, no study has so far been conducted to assess the safety and efficacy of licorice or triamcinolone acetonide mucoadhesive films on oral mucositis especially after RT. The previous studies have primarily addressed the preventive potentials of cryotherapy, sucralfate and phenyl butyrate on the occurrence of radiation-induced oral mucositis.

Yen et al. conducted a study regarding preventive effects of phenyl butyrate mouthwash on oral mucositis during RT or chemotherapy in patients with HNC. In this study, 36 HNC patients were randomized to standard oral care plus 5 mL of either phenyl butyrate 5% mouthwash (n = 17) or placebo (mouthwash vehicle, n = 19) taken four times daily. Treatment began when mild mucositis (Radiation Therapy Oncology Group grade 1) occurred and ended 4 weeks after RT completion. Safety and efficacy were based on adverse events, physical examination, laboratory determinations, vital signs, Oral Mucosa Assessment Scale, and the WHO

### Table 2  Comparison of the mean variables and baseline characteristics of the study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Triamcinolone (n: 30)</th>
<th>Licorice (n: 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain score</td>
<td>Week 0: 5.36 ± 1.29</td>
<td>Week 0: 2.20 ± 2.02</td>
<td>0.918</td>
</tr>
<tr>
<td></td>
<td>Week 1: 4.83 ± 1.91</td>
<td>Week 1: 4.80 ± 2.23</td>
<td>0.951</td>
</tr>
<tr>
<td></td>
<td>Week 2: 4.56 ± 1.67</td>
<td>Week 2: 4.70 ± 1.66</td>
<td>0.758</td>
</tr>
<tr>
<td></td>
<td>Week 3: 2.80 ± 2.15</td>
<td>Week 3: 2.60 ± 1.84</td>
<td>0.701</td>
</tr>
<tr>
<td></td>
<td>Week 4: 2.20 ± 2.02</td>
<td>Week 4: 2.08 ± 1.90</td>
<td>0.640</td>
</tr>
<tr>
<td>P-value</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Mucositis grade</td>
<td>Week 0: 2.40 ± 0.49</td>
<td>Week 0: 2.36 ± 0.49</td>
<td>0.792</td>
</tr>
<tr>
<td></td>
<td>Week 1: 2.10 ± 0.84</td>
<td>Week 1: 1.93 ± 0.83</td>
<td>0.438</td>
</tr>
<tr>
<td></td>
<td>Week 2: 2 ± 0.74</td>
<td>Week 2: 1.90 ± 0.71</td>
<td>0.597</td>
</tr>
<tr>
<td></td>
<td>Week 3: 1.33 ± 0.80</td>
<td>Week 3: 1.30 ± 0.79</td>
<td>0.848</td>
</tr>
<tr>
<td></td>
<td>Week 4: 0.96 ± 0.81</td>
<td>Week 4: 0.93 ± 0.78</td>
<td>0.875</td>
</tr>
<tr>
<td>P-value</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58.53 ± 8.89</td>
<td>57.33 ± 10.05</td>
<td>0.626</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 18 (60%)</td>
<td>19 (63.3%)</td>
<td>0.791</td>
</tr>
<tr>
<td></td>
<td>Female 12 (40%)</td>
<td>11 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes 14 (46.7%)</td>
<td>15 (50%)</td>
<td>0.796</td>
</tr>
<tr>
<td></td>
<td>No 16 (53.3%)</td>
<td>15 (50%)</td>
<td></td>
</tr>
<tr>
<td>Denture</td>
<td>Yes 19 (63.3%)</td>
<td>18 (60%)</td>
<td>0.791</td>
</tr>
<tr>
<td></td>
<td>No 11 (36.7%)</td>
<td>12 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

![Figure 1](image)  

**Figure 1** Line chart of the mean based on the groups. (—) triamcinolone; (—) licorice.
scores, the ability to eat, body weight change, local control and survival. They concluded that phenylbutyrate significantly decreases the impact of OM in HNC patients receiving RT or chemoradiotherapy and did not confront the tumor control.25

In a randomized controlled trial, Katranci et al. evaluated the effect of cryotherapy in preventing oral mucositis associated with chemotherapy. The study included 60 patients; 30 patients in the study group were instructed to hold ice cubes in their mouth shortly before, during and shortly after infusion of 5-FU with leucovorin, the 30 patients in the control group received routine care. They found that oral cryotherapy has a significant contribution to the protection of oral health by reducing mucositis score according to the WHO mucositis scale.26

Epstein and coworkers assessed the efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy. They concluded that prophylactic oral rinsing with sucralfate did not prevent oral ulcerative mucositis. Sucralfate may reduce the experience of pain during radiation therapy.5

In our study, we compared the efficacy and safety of a steroid versus an herbal agent regarding the management of radiation-induced mucositis. Meanwhile, the results in this pilot study provide initial support that the oral mucoadhesive films offer some promise in reducing oral mucositis for adult cancer patients undergoing RT. However, the small sample size available for the study limits the generalizability of the results. Furthermore, we recommend a similar study to be accomplished with regard to prevention and management of chemotherapy-induced oral mucositis.

It has been known for many decades that licorice root (Glycyrrhiza) includes an ingredient that speeds the healing of ulcers in the stomach. It is not yet known which ingredient in licorice root is responsible. More recently, it has been discovered that a majority of stomach ulcers are caused by bacteria called Helicobacter pylori and that most stomach ulcers are therefore treatable with pharmaceutical antibiotics. This suggests that the active ingredient in licorice root is an antimicrobial that interferes with the H. pylori bacteria or with a reaction of stomach tissues to the bacteria.18–20,23,24

Oral mucositis may have significant impact on the patient, is a dose- and rate-limiting complication of radiation therapy, and may necessitate changes in radiation treatment planning. Further study is needed to demonstrate the benefit of licorice in reducing pain associated with ulcerative mucositis in radiation treatment regimens of lower total dose or of more protracted course. Study is needed to assess the possible effect of medication upon adherence of oral pathogens and upon local oral infection, and in assessment of the potential to reduce systemic infection in immunocompromised patients with ulcerative mucositis. Licorice mucoadhesive films may be considered for palliation of pain when oral ulceration is present. Combinations of topical agents with licorice including antimicrobials should also be considered due to the known adherence of licorice mucoadhesive films to the gingival or buccal mucosa.

In Egypt, Ismail et al. prepared a standard concentration from lyophilized licorice extract (5% w/v) and used it as a mouthwash before and immediately after each session of radiation therapy. They encouraged the patients to repeat this mouthwash and swallow it several times throughout the day. The mucositis grade was reported according to the WHO grading system. Six weeks after the end of radiation, the flow of saliva in 5 min was measured for the flow in response to citric acid stimulation within 5 min; and the Na, Cl and bicarbonate content would be measured. Forty-five patients with H&N tumors of different sites were all treated with

Figure 2 Bar chart demonstrating the percent and frequency of mucositis. (■) grade 0; (□) grade 1; (▲) grade 2; (●) grade 3.
irradiation. They concluded that the use of licorice in H&N tumors is safe and prevents radiation-induced mucositis that may result in better outcome.27

Considering the fact that cancer patients generally have systemic problems, and the systemic side effects that corticosteroids impose on the one hand, and the lack of meaningful difference between triamcinolone acetonide and licorice, a herbal agent without obvious adverse effects, on the other hand, it can be advised to use licorice mucoadhesive films instead of triamcinolone acetonide mucoadhesive films in terms of managing RT-induced mucositis. Interestingly, the analysis of the questionnaires filled by the patients or their family members showed an inclination toward herbal agents, which again supports the need for more immediate studies regarding licorice and similar herbal drugs.

Further evaluation in randomized study is urgently required to conclude in this new modality.

Limitations
Like other researches in this field, this study has several limitations.29 The study was conducted in specific state run cancer care settings and the results are therefore only applicable to this specific patient population. Convenience sampling was used for sample selection, which could have led to bias. Using a questionnaire as a data collection instrument allowed the respondents to not answer all the questions. In view of the fact that most cancer patients may have mood fluctuations during RT, their responses to our questions in terms of pain score might be influenced. Of note, the assessment of WHO scales 2 and 3 in the patients with laryngeal cancer who may already have dysphagia related to their cancer location would have been impaired.

ACKNOWLEDGMENT
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REFERENCES
APPENDIX I
CONSORT FLOW DIAGRAM

Enrollment
Assessed for eligibility (n= 97)
  Excluded (n=37)
    • Not meeting inclusion criteria (n= 9)
    • Declined to participate (n= 22)
    • Other reasons (n= 6)

Randomized (n= 60)

Allocation
Allocated to intervention (n= 30)
  • Received allocated intervention (n= 30)
  • Did not receive allocated intervention (n=0)

Allocated to intervention (n= 30)
  • Received allocated intervention (n= 30)
  • Did not receive allocated intervention (n=0)

Follow-Up
Lost to follow-up (n= 0)
Discontinued intervention (n= 0)

Lost to follow-up (n= 0)
Discontinued intervention (n= 0)

Analysis
Analysed (n=30)
  • Excluded from analysis (n= 0)

Analysed (n= 30)
  • Excluded from analysis (n= 0)